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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
NGUYEN, QUANG	

ART UNIT	PAPER NUMBER
1633	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/622,293	FREYMAN ET AL.	
	Examiner	Art Unit	
	QUANG NGUYEN, Ph.D.	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 October 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,5-8,10-26,30,34,35 and 43-45* is/are pending in the application.

4a) Of the above claim(s) *16-26 and 34* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 5-8, 10-15, 30, 35 and 43-45* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendment filed on 10/22/2010 was entered.

Claims 1, 5-8, 10-26, 30, 34-35 and 43-45 are pending in the present application.

Applicants elected previously Group I, drawn to a method for producing a decellularized extracellular matrix material containing a biological material or for producing a tissue regeneration scaffold for implantation into a patient wherein the step of conditioning a body tissue of a donor animal by genetic engineering and allowing the conditioned body tissue to produce the biological material are conducted prior to harvesting the conditioned body tissue from the donor animal. Applicants further elected the following species with traverse in the reply filed on 9/19/05, (a) bone marrow as a species of a body tissue; (b) VEGF as a species of a biological material; and (c) human as a species of a donor animal.

This application contains claims 16-26 and 34 drawn to an invention nonelected without traverse in the reply filed on 9/19/05.

Accordingly, amended claims 1, 5-8, 10-15, 30, 35 and 43-45 are examined on the merits herein with the aforementioned elected species.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Amended claims 1, 5, 8, 10-12, 14-15, 35 and 43-45 are rejected under 35 U.S.C. 103(a) as being unpatentable over Naughton (US 5,830,708; IDS) in view of Mitchell et al (US 2002/0115208), Patel et al. (US 7,087,089) and Wolff et al. (WO 99/55379; IDS) for the same reasons already set forth in the Office action mailed on 7/23/2010 (pages 3-9). ***The same rejection is restated below.***

With respect to the elected species, Naughton teaches a method for producing a composition containing naturally secreted human extracellular matrix material, said method comprises the steps of: (a) culturing extracellular matrix secreting human stromal cells (e.g., fibroblast endothelial cells, macrophages/monocytes, adipocytes and reticular cells) from tissues/organs obtained by appropriate biopsy or upon autopsy, including aspirated **bone marrow from normal human adult volunteers** (col. 5, lines 48-54; col. 9, lines 12-17; col. 15, lines 7-9), on a biocompatible three dimensional framework *in vitro*; (b) the stromal cells are killed after secretion of the extracellular matrix onto the framework and **the cells and cellular contents are removed from the framework by different ways including killing the cells by flash freezing the living stromal tissue prepared *in vitro* in liquid nitrogen without a cryopreservative, or with sterile water such that the cells burst in response to osmotic pressure and the cellular debris is removed by a mild detergent rinse such as EDTA (a protease inhibitor for metalloproteinases such as collagenases)**, CHAPS or a switterionic detergent (col. 11, line 62 continues to line 31 of col. 12); and (c) the extracellular matrix material deposited on the framework is collected in a variety of ways depending on

whether the three-dimensional framework is composed of material that is biodegradable or non-biodegradable (col. 12, lines 32-63). Naughton stated "**None of the removal processes are designed to damage and/or denature the naturally secreted human extracellular matrix produced by the cells**" (col. 12, lines 61-63). Naughton also teaches that **it may be desirable to prepare an extracellular matrix containing a foreign gene product, growth factor, regulatory factor and in such a situation the cells are genetically engineered to express the gene product that is immobilized in the extracellular matrix laid down by the stromal cells** (col. 10, line 59 continues to line 22 of col. 11). **This is a conditioning step**. Moreover, biologically active substances such as proteins and drugs can also be further incorporated in a formulation comprising naturally secreted extracellular matrix for release or controlled release of these active substances after injection of the composition that include tissue growth factors such as TGF-beta and the like which promote healing and tissue repair at the site of injection (col. 13, lines 12-22). Furthermore, Naughton teaches that **the naturally secreted extracellular matrix preparation is capable of promoting connective tissue deposition, angiogenesis, reepithilialization and fibroplasias, which is useful in the repair of skin and other tissue defects** (col. 3, lines 43-48). Exemplifications showed that **cells were cultured for at least 5-7 days, with a change of fresh media every 3-4 days** (see examples). It should be noted that the term "body tissue" is defined by the instant specification broadly encompasses any or a number of cells, tissues or organs (see instant specification on page 7, lines 7-8).

Naughton does not specifically teach a method for producing a decellularized extracellular matrix containing a growth factor, comprising the step of conditioning (**genetic engineering is the elected invention**) a body tissue (**bone marrow is the elected species**) of a donor animal (**human is the elected species**) ***in vivo*** to produce a growth factor **prior to the step of harvesting the conditioned body tissue from the donor animal and decellularizing the conditioned body tissue**.

At the effective filing date of the present application (7/17/2003), Mitchell et al also disclosed methods for producing decellularized tissue engineered constructs and decellularized engineered native tissues for implanting into an individual in need thereof (see at least the abstract; Summary of the Invention), and taught that although in general the production of the tissue engineered construct involves culturing the developing tissue primarily *in vitro*, **tissue engineered constructs produced at least in part by culturing the tissue *in vivo* are also contemplated** (page 5, bottom of paragraph 67). Mitchell et al further taught that **there is a need to expose developing tissue engineered constructs to certain stimuli, so that the resulting construct develops properties and structure that more closely resemble those of the corresponding naturally occurring tissue** (paragraph 96).

Moreover, Patel et al already taught a process for preparing acellular extracellular matrix materials useful for supporting cell growth *in vivo* and *in vitro* (see at least Summary of the Invention). Patel et al also disclosed that **the acellular collagen-containing extracellular matrices can be derived from renal capsular tissues harvested from either transgenic animals (pre-conditioned genetically modifying**

donor animal) or non-transgenic animals, and that animals encompass mammals, preferably porcine, bovine or ovine (col. 3, lines 11-21). Patel et al further taught specifically **the use of a hypertonic decellularization solution such as 1.0 N saline or EDTA which is an inhibitor for a metalloproteinase such as a collagenase**; and that **a decellularization technique which does not affect the mechanical strength and retains advantageous cell growth promoting properties of the extracellular matrix is preferred** (see at least col. 5, lines 45-54; and col. 3, lines 45-67).

Furthermore, Wolff et al also disclosed **a process for delivering a polynucleotide encoding a protein of interest (e.g., hormones, cytokines, growth factors and others) into parenchymal cells within tissues *in situ* and *in vivo*, including parenchymal cells of bone marrow within a mammal** (see at least Summary of the Invention; and page 8, second paragraph; page 7, first paragraph). Additionally, Wolff stated "In spleen, thymus, lymph nodes and **bone marrow, the parenchymal cells include recitular cells and blood cells (or precursors to blood cells) such as lymphocytes, monocytes, plasma cells and macrophages**" (page 8, lines 4-6). **Exemplifications showed that expression of a transgene was assessed 2 days after vector injection into a treated mammal** (see at least page 14, lines 10-25; page 51, lines 8-18).

Accordingly, it would have been obvious for an ordinary skilled artisan in the art to modify the teachings of Naughton by also preparing a decellularized bone marrow extracellular matrix material using bone marrow stromal/parenchymal cells **(falling within the broad scope of the term "body tissue" as defined by the present**

application as set forth above) from a pre-conditioned donor animal, including a pre-conditioned human donor, whose parenchymal cells of the bone marrow had been transfected with a polynucleotide encoding a protein of interest such as a growth factor, for healing and/or repairing tissues in a patient in need thereof at least in light of the teachings of Patel et al. and Wolff et al. Alternatively, it would also have been obvious for an ordinary skilled artisan in the art to modify the teachings of Naughton by also preparing a decellularized bone marrow extracellular matrix directly harvested from the bone marrow of a donor animal, including a human donor, whose bone marrow parenchymal cells have been transfected *in vivo* with a polynucleotide encoding a growth factor, for healing and/or repairing tissues in a patient in need thereof in light of the teachings of Mitchell et al, Patel et al. and Wolff et al. as discussed above.

An ordinary skilled artisan would have been motivated to carry out the above modifications because Patel et al already taught that acellular extracellular matrix materials useful for supporting cell growth *in vivo* and *in vitro* could be harvested from either a transgenic animal (a pre-conditioned genetically modifying donor) or a non-transgenic animal. Additionally, Wolff et al already disclosed successfully a process for delivering a polynucleotide encoding any protein of interest in parenchymal cells of bone marrow within a mammal, including a polynucleotide encoding a growth factor. Moreover, by harvesting already *in vivo* transfected bone marrow parenchymal cells from a pre-conditioned animal donor or a pre-conditioned human donor, there is no further need to transfect bone marrow stromal/parenchymal cells cultured on a biocompatible three dimensional framework *in vitro* as contemplated explicitly by

Naughton. Furthermore, an ordinary skilled artisan would also have been motivated to prepare a decellularized bone marrow extracellular matrix harvested directly from the bone marrow of a donor animal, including a human donor, whose bone marrow parenchymal cells have been transfected *in vivo* with a polynucleotide encoding a growth factor because Mitchell et al already taught that unlike the decellularized extracellular matrix prepared *in vitro* or in cultured conditions, **such a preparation of an *in vivo* conditioned bone marrow extracellular matrix would have properties, constituents and structure more resembling to those of a naturally occurring bone marrow extracellular matrix together with the further incorporation of a desired growth factor**. Moreover, Patel et al already taught that acellular extracellular matrix materials useful for supporting cell growth *in vivo* and *in vitro* could be harvested from a transgenic animal (a pre-conditioned genetically modifying donor).

An ordinary skilled artisan would have a reasonable expectation of success to carry out the above modifications in light of the teachings of Naughton, Mitchell et al, Patel et al., and Wolff et al., coupled with a high level of skills of an ordinary skilled artisan in the relevant art.

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Claims 13 and 30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Naughton (US 5,830,708; IDS) in view of Mitchell et al (US 2002/0115208), Patel et al. (US 7,087,089) and Wolff et al. (WO 99/55379; IDS) as applied to claims 1, 5, 8,

10-12, 14-15, 35 and 43-45 above, and further in view of Herlyn et al. (WO 98/39035; Cited previously) for the same reasons already set forth in the Office action mailed on 7/23/2010 (pages 9-10). ***The same rejection is restated below.***

The combined teachings of Naughton, Mitchell et al, Patel et al. and Wolff et al. were presented above. However, none of the references teaches specifically that bone marrow is transfected with a nucleic acid encoding VEGF **(elected species)**.

However, at the effective filing date of the present application Herlyn et al already taught growth factors, particularly VEGF is useful in wound repair in mammalian tissue by enhancing fibroblast growth and formation into a matrix, enhancing keratinocyte growth and angiogenesis and *ex vivo* method for infecting tissue to be transplanted with a recombinant virus expressing VEGF prior to transplantation (at least page 6, lines 14-23).

Accordingly, it would have been obvious for an ordinary skilled artisan in the art to further modify the combined method of Naughton, Patel et al. and Wolff et al. by also selecting VEGF as the growth factor gene product to be incorporated into the decellularized extracellular matrix in light of the teachings of Herlyn et al.

An ordinary skilled artisan would have been motivated to carry out the above modification because Herlyn et al already taught growth factors, particularly VEGF is useful in wound repair in mammalian tissue by enhancing fibroblast growth and formation into a matrix, enhancing keratinocyte growth and angiogenesis, and that this would enhance the clinical value for the composition containing the decellularized

extracellular matrix material resulting from the combined teachings of Naughton, Patel et al. and Wolff et al.

An ordinary skilled artisan would have a reasonable expectation of success to carry out the above modification in light of the teachings of Naughton, Mitchell et al, Patel et al. Wolff et al., and Herlyn et al., coupled with a high level of skills of an ordinary skilled artisan in the relevant art.

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Claims 6-7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Naughton (US 5,830,708; IDS) in view of Mitchell et al (US 2002/0115208), Patel et al. (US 7,087,089) and Wolff et al. (WO 99/55379; IDS) as applied to claims 1, 5, 8, 10-12, 14-15, 35 and 43-45 above, and further in view of Schwarz et al. (US 6,656,916) for the same reasons already set forth in the Office action mailed on 7/23/2010 (pages 10-12). ***The same rejection is restated below.***

The combined teachings of Naughton, Mitchell et al, Patel et al. and Wolff et al. were presented above. However, none of the references teaches specifically that a further step of delivering a therapeutic agent to the body tissue before or after the conditioning step.

However, at the effective filing date of the present application, Schwartz et al already taught **a method of increasing the cellular expression of a gene in a biological tissue in an animal, including a bone marrow in a human**, said method

comprises administering to said animal a pharmacologically effective dose of a glucocorticoid in an amount sufficient to increase the cellular expression of said gene (see at least col. 2, lines 35-51; col. 5, lines 54-59). Schwartz et al taught specifically that any glucocorticoid such as hydrocortisone, prednisone, prednisolone, triamcinolone, betamethasone, budesonide, flunisolide and dexamethasone can be used (col. 5, lines 31-37). The glucocorticoid may be administered concurrently with the delivery of the gene, **prior to the delivery of the gene or after delivery of the gene** (col. 5, lines 48-51).

Accordingly, it would have been obvious for an ordinary skilled artisan in the art to further modify the combined method of Naughton, Mitchell et al, Patel et al. and Wolff et al. by also administering to the donor animal a therapeutic agent such as a glucocoritoid to a body tissue prior to or after the gene delivery in light of the teachings of Schwarz et al.

An ordinary skilled artisan would have been motivated to carry out the above modification because the administration of a therapeutic agent such as a glucocorticoid prior to or after the delivery of a gene would enhance the cellular expression of a delivered gene in a biological tissue, including a bone marrow in a human, as taught by Schwartz et al.

An ordinary skilled artisan would have a reasonable expectation of success to carry out the above modification in light of the teachings of Naughton, Mitchell et al, Patel et al., Wolff et al. and Schwarz et al., coupled with a high level of skills of an ordinary skilled artisan in the relevant art.

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Response to Arguments

Applicants' arguments related to the above rejections in the Amendment filed on 10/22/2010 (pages 8-12) have been fully considered but they are respectfully not found persuasive for the reasons discussed below.

Once again, Applicants argue that the Naughton reference does not describe decellularizing a conditioned body tissue harvested from a donor animal; and that none of additional references of Mitchell, Patel, Wolff, Herlyn and Schwarz cures this deficiency. Applicants further argue that the claimed method is more than simply the combination of just any conditioning process, for increasing just any growth factor in the extracellular matrix, with just any decellularizing process. In the claimed method, there is a synergistic, functional relationship between the growth factors, the extracellular matrix that can serve as a storage depot for growth factors, and the decellularizing step using a protease inhibitor that work together to produce an extracellular matrix material having an improved ability to treat a patient's diseased or damaged body tissue. Additionally, the decellularizing step using a protease inhibitor works in conjunction with the increased growth factors present in the extracellular matrix because proteases released from lysed or disrupted cells may cause the unwanted, premature release of the growth factors from the extracellular matrix and the growth factors would be lost and rendering the work performed in conditioning the body tissue to increase growth factor

production would be negated. Thus, the invention of claims 1 and 35 is more than just the sum of its part.

Applicants further submitted the report by Badylak (Transplant Immunology 12:367-377, 2004) which demonstrates that the three-dimensional organization of the growth factors that results from the claimed invention provides an advantage that was not appreciated until after the date of the invention. For examples the cited statements "The three-dimensional organization of these molecules distinguishes ECM scaffolds from synthetic scaffold materials and is associated with constructive tissue remodeling instead of scar tissue"; "The bioactive molecules that reside within the ECM and their unique spatial distribution provide a reservoir of biologic signals"; and "An advantage of utilizing the ECM in its native state as a substrate or scaffold for cell growth and differentiation is the presence of all the attendant growth factors (and their inhibitors) in the same relative amounts that exist in nature and perhaps more importantly, in their native three-dimensional ultrastructure" demonstrated that the result obtained by the claimed invention is more than simply the sum of its part that was unappreciated by the art at the time of the claimed invention. With respect to claim 44, Applicants also argued that none of the cited references teaches the limitation "the conditioned body tissue is allowed to produce the growth factor *in vivo* for at least 2 days prior to harvesting the conditioned body tissue from the donor animal".

Firstly, please note that the above rejections were made under 35 U.S.C. 103(a), and therefore there is no requirement that each of the cited references has to teach every limitation of the claims, particularly with respect to the elected species.

Additionally, with respect to the issue that there is no specific suggestion or teaching in anyone of the cited references to combine, please also note that KSR forecloses the argument that a **specific** teaching, suggestion, or motivation is required to support a finding of obviousness. See the recent Board decision *Ex parte Smith*, --USPQ2d--, slip. op. at 20, (Bd. Pat. App. & Interf. June 25, 2007).

Secondly, the instant specification defines **the term "body tissue" to encompass any or a number of cells, tissues or organs** (see instant specification on page 7, lines 7-8). Therefore, as written the instant claims encompass at least cells as a body tissue of a donor animal, and particularly bone marrow cells as the elected species. Please also note that cells also possess their own histoarchitecture and/or "peripheral" cellular extracellular microstructure. As already set forth in the above rejections, it would have been obvious for an ordinary skilled artisan in the art to modify the teachings of Naughton by also preparing a decellularized bone marrow extracellular matrix material using bone marrow stromal/parenchymal cells **(falling within the broad scope of the term "body tissue" as defined by the present application as set forth above)** from a pre-conditioned donor animal, including a pre-conditioned human donor, whose parenchymal cells of the bone marrow had been transfected with a polynucleotide encoding a protein of interest such as a growth factor, for healing and/or repairing tissues in a patient in need thereof at least in light of the teachings of Patel et al. and Wolff et al.. Alternatively, it would also have been obvious for an ordinary skilled artisan in the art to modify the teachings of Naughton by also preparing a decellularized bone marrow extracellular matrix directly harvested from the bone marrow of a donor

animal, including a human donor, whose bone marrow parenchymal cells have been transfected *in vivo* with a polynucleotide encoding a growth factor, for healing and/or repairing tissues in a patient in need thereof in light of the teachings of Mitchell et al, Patel et al. and Wolff et al. An ordinary skilled artisan would have been motivated to carry out the above modifications because Patel et al already taught that acellular extracellular matrix materials useful for supporting cell growth *in vivo* and *in vitro* could be harvested from either a transgenic animal (a pre-conditioned genetically modifying donor) or a non-transgenic animal. Additionally, Wolff et al already disclosed successfully a process for delivering a polynucleotide encoding any protein of interest in parenchymal cells of bone marrow within a mammal, including a polynucleotide encoding a growth factor. Moreover, by harvesting already *in vivo* transfected bone marrow parenchymal cells from a pre-conditioned animal donor or a pre-conditioned human donor, there is no further need to transfect bone marrow stromal/parenchymal cells cultured on a biocompatible three dimensional framework *in vitro* as contemplated explicitly by Naughton. Furthermore, an ordinary skilled artisan would also have been motivated to prepare a decellularized bone marrow extracellular matrix harvested directly from the bone marrow of a donor animal, including a human donor, whose bone marrow parenchymal cells have been transfected *in vivo* with a polynucleotide encoding a growth factor because Mitchell et al already taught that unlike the decellularized extracellular matrix prepared in vitro or in cultured conditions, such a preparation of an *in vivo* conditioned bone marrow extracellular matrix would have properties, constituents

and structure more resembling to those of a naturally occurring bone marrow extracellular matrix together with the further incorporation of a desired growth factor.

Thirdly, the additional citation of the Herlyn et al and Schwartz et al references is to further supplement the combined teachings of Naughton, Mitchell et al, Patel et al and Wolf et al for additionally limitations recited in dependent claims 6-7, 13 and 30.

Fourthly, both independent claims 1 and 35 recite "wherein the decellularization involves the use of a protease inhibitor"; and since the primary Naughton reference teaches explicitly that the stromal cells are killed after secretion of the extracellular matrix onto the framework and **the cells and cellular contents are removed from the framework by different ways including killing the cells by flash freezing the living stromal tissue prepared in vitro in liquid nitrogen without a cryopreservative, or with sterile water such that the cells burst in response to osmotic pressure and the cellular debris is removed by a mild detergent rinse such as EDTA which is a protease inhibitor for metalloproteinases such as collagenases.** The removal of cellular debris is a part of a decellularization process, and it involves clearly the use of a protease inhibitor. Moreover, Naughton stated "**None of the removal processes are designed to damage and/or denature the naturally secreted human extracellular matrix produced by the cells**" (col. 12, lines 61-63). Furthermore, Patel et al also taught specifically **the use of a hypertonic decellularization solution such as 1.0 N saline or EDTA which is an inhibitor for a metalloproteinase such as a collagenase**; and that **a decellularization technique which does not affect the mechanical strength and retains advantageous cell growth promoting properties**

of the extracellular matrix is preferred (see at least col. 5, lines 45-54; and col. 3, lines 45-67). It was also known in the prior art that extracellular matrix can serve as a local depot for the storage of growth factor as evidenced at least by the teachigns of Taipale et al (FASEB Journal 11, 1997; Cited by Applicants). Accordingly, there is nothing that is unexpected or surprising or any unexpected synergistic effects or anything more than the sum of its parts obtained by the methods as broadly claimed.

Fifthly, **although it is not a requisite**, with respect to the elected species it is noted that there is no actual example that Applicants have actually transfected bone marrow of a human donor with a polynucleotide encoding VEGF, harvested the transfected bone marrow and decellularized the harvested bone marrow to obtain an extracellular matrix material containing VEGF.

Sixthly, with respect to the cited Badylak reference which is a review article on xenogeneic extracellular matrix as a scaffold for tissue reconstruction it should be noted that the article is completely silent about any conditioning (e.g., *in vivo* genetically engineering) of a body tissue of a donor animal prior to harvesting xenogeneic extracellular matrix to be used as a scaffold for tissue reconstruction. Additionally, there is nothing in the Badylak reference that indicates or even suggests any result that was not appreciated and/or unexpected and/or surprising at the effective filing date of the present application. At least, Mitchell et al already taught that **there is a need to expose developing tissue engineered constructs to certain stimuli, so that the resulting construct develops properties and structure that more closely resemble those of the corresponding naturally occurring tissue** (paragraph 96). This

teaching indicates clearly that at the effective filing date of the present application, an ordinary skill artisan already appreciated the "superiority" of the structure and/or properties of a naturally occurring tissue relative to any *in vitro* and/or artificial tissue engineered constructs. Moreover, in the preparation of acellular collagen-containing extracellular matrices derived from renal capsular tissues harvested from either transgenic animals (pre-conditioned genetically modifying donor animal) or non-transgenic animals; Patel et al also explicitly taught that **any decellularization technique which does not affect the mechanical strength and retains advantageous cell growth promoting properties of the extracellular matrix is preferred; indicating the desirability to retain intact structure and/or properties of naturally occurring extracellular matrix obtained from transgenic and/or non-transgenic animals**.

Seventhly, it appears that Applicants did not take into considerations the overall teachings of all of the cited references, but focused instead on the teaching of each cited reference in isolation one from the others. For example, with respect to the limitation recited in claim 44, please note that Wolff et al already taught by exemplifications disclosing **that expression of a transgene was assessed 2 days after vector injection into a treated mammal** (see at least page 14, lines 10-25; page 51, lines 8-18).

Conclusion

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (571) 272-0776.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's SPE, Joseph T. Woitach, Ph.D., may be reached at (571) 272-0739.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1633; Central Fax No. (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

/QUANG NGUYEN/
Primary Examiner, Art Unit 1633